REMARKS

Claims 1-36 are pending in this application. Claims 1-11 and 15-36 are withdrawn as being drawn to a non-elected invention. Claims 12-14 are rejected. By the present amendment claims 12 and 13 are amended for clarity, claims 1-11 and 15-36 are hereby canceled without prejudice or disclaimer, and new claim 37 is hereby added. As they are fully supported by the original specification, the amendments and new claim add no new matter.

In view of the above-described amendments and following remarks, reconsideration of claims 12-14, and consideration of new claim 37 are respectfully requested.

Section 112 Rejections

Claims 12-14 are rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement.

Claim 12 has been amended to recite a transgene that comprises nucleotide -507 to nucleotide +1 of the human FGF1B promoter, a sequence that was known in the art at the time the present application was filed. (See page 7, lines 23-26 of the present application, which indicates that the human FGF1B promoter was disclosed in GenBank Accession No. Z14150.) In addition, the sequence that extends from nucleotide -507 to nucleotide +1 and from nucleotide -540 to nucleotide +31 of the human FGF1B promoter is shown in Figure 10 and SEQ ID NO. 2 of the present application. Accordingly, applicants submit that amended claims 12 to 14 of the present application comply with the written description requirement.

New claim 37 recites a construct that comprises the mouse FGF1B promoter operably linked to a sequence encoding the large SV40 T antigen . The sequence of the mouse FGF1B promoter was also known at the time the present application was filed, and was disclosed in GenBank Accession No. U67609. (See page 7, lines 25-29 of the present application.) In addition, this sequence was published in Alam et al, J Biol. Chem. (1996) vol. 271:30263-30271 (hereinafter "Alam et al."), a reference cited by the Patent Office in the §103 rejection of claims 12-14. Thus, Applicants, as well as those of ordinary skill in the art, were in possession of the sequence of the mouse FGF1 B promoter at the time the present application was filed.

Claims 12-14 have been rejected under §112, second paragraph as being indefinite. Since one of ordinary skill in the art knew the sequence of the human FGF1B promoter at the time the present application was filed and would appreciate that the numbering scheme recited in

amended claim 12 and original claim 13 of the present application is based upon the transcription initiation site (i.e, in the art +1 is considered to be the transcription initiation site), Applicants respectfully disagree that the phrase "nucleotide -540 to + 31 of the human FGF1B gene" is indefinite. Nonetheless, to expedite prosecution of the application, Applicants have amended claims 12 and 13 to identify the nucleotides in SEQ ID NO. 2 that correspond to nucleotide -507 to +1, and nucleotide -540 to +31, respectively, in the FGF1 B promoter. Support for the amendment is found in Figure 10, page 6, lines 9-11, and on page 13, lines 13-29 of the instant application.

Section 103 Rejection

Claims 12 to 14 are rejected under 35 U.S.C. § 103 as being unpatentable over Alam et al. or Ray et al. (The Journal of Biochemistry. Vol. 272: 7456-7555, 1997)(hereinafter Ray et al.) in view of Takahashi et al (Exp. Anim. 48: 255-261, 1999) (hereinafter "Takahashi") and Perraud et al (Oncogene Vol. 7: 993-997, 1992) (hereinafter "Perraud") and Ausubel et al (Short Protocols in Molecular Biology. 3rd edition 1992, page 9-28-9-30, John Wiley and Sons. (hereinafter "Ausubel"). The Patent Office stated:

> Alam et al and Ray et al teach the characterization of the FGF1B promoter...None of these arts teaches a DNA construct comprising a transgene comprising an FGF1B promoter linked to SV40 large T antigen.
>
> Takahashi et al teaches rat cell lines in which expression of SV40 T antigen was under control of a promoter and the cell lines were isolated from transgenic rats that were produced by integrating the construct comprising SV40 promoter driving expression of the SV40 T antigen.....Perraud et al teaches the construction of vectors comprising a promoter driving expression of SV40 long T antigen to study the potential oncogenesis associated with tissue-specific activity of the promoter for CFTR gene..
>
> At the time of the invention, it would have been obvious to an artisan of ordinary skill to modify the vectors of Ray et al or Alam et al by replacing the reporter gene with the SV40 T antigen with a reasonable expectation of success. An artisan would have been motivated to make such constructs to study the brain specific expression of the FGF1B promoter and make cell lines or transgenic mice or rats which could provide an in vivo model for studying the promoter function.

As admitted by the Patent Office Alam et al and Ray et al do not teach a DNA construct comprising an FGF1B promoter linked to an SV40 T antigen coding sequence. Indeed, Alam et al do not even teach a DNA construct comprising an FGF1B promoter linked to any heterologous protein coding sequence, much less the SV40 T antigen coding sequence. Moreover, Takahashi, Perroud and Ausubel do not provide the motivation to modify the DNA

constructs of Ray et al by replacing the luciferase encoding sequence with an SV40 T antigen encoding sequence. These secondary references also do not provide a reasonable expectation that once could introduce the construct of claim 12 into the genome of a transgenic animal and obtain an animal model useful for studying brain specific expression of the FGF1B promoter.

Takahashi is directed to introducing constructs comprising the SV40 promoter operably linked to a sequence encoding a temperature-sensitive (ts) SV40 antigen in order to obtain differentiated immortalized cells. (See last paragraph in the Introduction of Takahashi.) The promoter of the Takahasi construct is not a tissue-specific promoter. The coding sequence of the Takahashi construct encodes a temperature sensitive antigen, which is different from the SV40 T antigen recited in claims 12-14. Thus, even if one were to replace the reporter gene of the DNA constructs of Alam with the coding sequence of the Takahashi construct, one would not achieve the construct recited in claims 12 to 14 of the present invention.

Perraud obtained transgenic animals by incorporating a DNA molecule comprising the CFTR promoter operably linked to an SV40 T antigen into the genome of such animals. However, the transgenic animals of Perraud did NOT express the SV40 T antigen in tissues where the CFTR promoter is known to be active. (See next to last sentence in Abstract of Perroud.) Indeed, Perraud specifically states "Based on clinical manifestations of CF, we expected that such an approach would permit the development of lung, pancreas and gastrointestinal epithelial tumors. Surprisingly, using a human CFTR promoter sequence fused to the SV40 early coding region as a reporter gene, the only tumors observed were ependymomas." (See last full paragraph on page 993 of Perraud, a complete copy of which is attached hereto for the Patent Office's convenience.) In other words, Perraud and his co-investigators did not observe expression of the SV40 T antigen in cells where the CFTR promoter is active when they incorporated their CFTR/SV40 T antigen coding sequence construct into the genome of animals. This shows that the earlier in vitro results obtained by these authors, in which the CFTR promoter drove expression of reporter genes in an epithelial cell line (See 1st and second sentences in the first full paragraph in the right hand column on page 993 of Perraud.) were not good predictors of their in vivo results. Thus, on the basis of Perraud one of ordinary skill in the art would not expect to observe SV40 T antigen expression in brain cells of transgenic animals whose genome comprises the human FGF1B promoter operably linked to an SV40 T antigen coding sequence. As a whole, Perraud appears to suggest just the opposite, namely that SV40 T antigen expression, if it occurs at all in transgenic animals whose

genomes comprise the construct of claim 12, would most likely occur in a tissue other than brain tissue.

Ausubel provides no teachings or suggestions that overcome the deficiencies of Takahashi or Perraud. Accordingly, claims 12-14, as amended, are not obvious over Alam et al or Ray et al in view of Takahashi, Perraud, and Ausubel.

Applicants submit that claims 12-14 as amended and new claim 37 are now in condition for allowance. Prompt notice of such allowance is respectfully requested.

Respectfully submitted,

Date: April 15, 2004

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